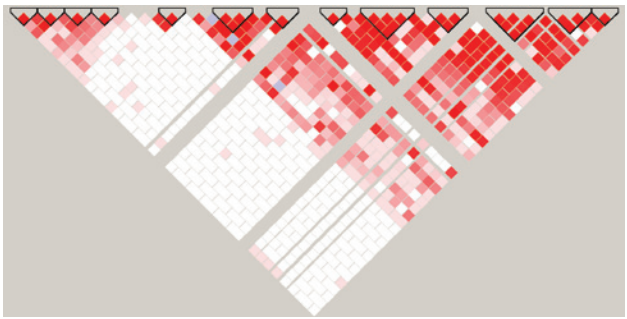
Cross-Cutting Research

Advances in medicine are largely dependent upon the accumulation of new knowledge about biologic processes, often at the smallest levels of an organism—its genes, the proteins they encode, and the workings of and communications between cells. In many cases, major strides in fighting disease can be traced back to laboratory studies whose immediate relevance to health could not have been fully known or appreciated at the time they were conducted. Opportunities to make exciting new discoveries and advances are arising ever more rapidly with the development of new technologies, new approaches, and even new scientific disciplines. Described here are studies that span scientific boundaries, including research on fundamental biologic processes as well as the development of new technologies that make such studies possible. The insights gained through this type of research can be expected to propel disease-oriented research, not only within the NIDDK mission, but also in many other fields, for today's cross-cutting advances may lead to tomorrow's new treatments.

Genome-wide Association and Other Genetic Studies: NIDDK-supported scientists have discovered many genetic variants that influence a person's likelihood of developing different diseases. Genetic findings have greatly accelerated in recent years as a result of the Human Genome Project and related efforts, including the development of the HapMap, a collection of many thousands of common genetic variants, called "SNPs," throughout the genome. Genome-wide association studies (GWAS) rely on these research tools and advanced technologies to identify genetic differences between people with specific illnesses and healthy individuals. In some cases, the genetic association maps to a chromosomal region that had not been thought to play a role in biological processes involved in the disease under study. Researchers have thus far identified over 40 genetic variants that are associated with an increased risk of type 1 diabetes, and over 30 genetic variants associated with increased risk of type 2 diabetes. One genetic region previously found to be strongly associated with type 2 diabetes has recently been implicated in a very different condition: prostate cancer. Scientists in the NIDDK-supported Inflammatory Bowel Disease (IBD) Genetics Consortium, together with other research teams, have identified over 30 genes and chromosomal regions



Data from a genome-wide association study of inflammatory bowel disease, which identified genetic variations associated with disease susceptibility. *Image credit:* Rioux J. et al. Reprinted by permission from Macmillan Publishers Ltd: *Nat Genet*, 39: 596-604, copyright 2007.

associated with Crohn's disease. Through another advanced approach to genetic analysis, also based on the HapMap and SNP data, researchers recently identified variations around the *MYH9* gene that may account for much of the increased burden of idiopathic focal segmental glomerulosclerosis (a type of kidney disease) and other non-diabetic kidney disease among African Americans. Other types of genetic studies over the past several decades have identified genes that influence diseases such as cystic fibrosis, pancreatitis, and forms of monogenic diabetes. These discoveries open up new avenues of research for disease prevention and treatment.

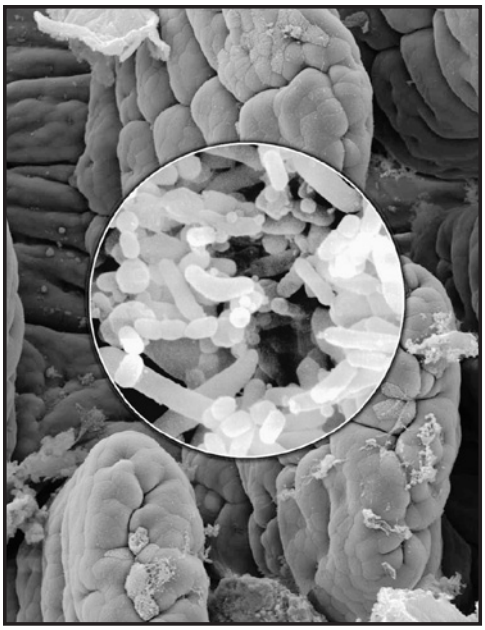
Nuclear Hormone Receptors: A broad range of metabolic, reproductive, developmental, and immune processes are regulated by a family of proteins called nuclear hormone receptors. These proteins respond to a variety of hormones by turning genes on or off, to modulate cell functions. The Nuclear Receptor Signaling Atlas (NURSA) is a trans-NIH initiative, led by the NIDDK, that funds scientists to develop a comprehensive understanding of the structure, function, and role in disease of nuclear hormone receptors. NURSA is focused on metabolism and the development of a number of metabolic disorders, including obesity, lipid dysregulation, and type 2 diabetes, as well as on processes of aging and hormone-dependent cancers. Researchers in the NURSA consortium have made key discoveries in the role of nuclear receptors in physiology and mechanisms of disease.

Pegylation: The addition of polyethylene glycol—"pegylation"—has emerged as a favored way to improve the staying power, and hence the effectiveness, of a variety of compounds used to treat conditions such as adenosine deaminase deficiency, hepatitis C, and other NIDDK-relevant diseases. Studies are under way to examine the possible benefits of pegylating insulin, to prolong its circulation time; antibodies for targeting of tumors; and other enzymes to aid in recovery from injury.

Regulating Cellular Traffic: NIDDK-supported studies have yielded important insights into the exquisitely organized transport of nutrients, hormones, and other molecules from within a cell to the cell's outer membrane, and between a cell and its surroundings. Scientists discovered how small cellular structures called vesicles carry this cargo and dock at the correct target locations. This research has improved our understanding of diverse biologic processes and illuminated the role of vesicle transport in diseases such as type 2 diabetes and cystic fibrosis.

Role of "Autophagy" in NIDDK-related Diseases: Autophagy is a process that cells use to degrade and recycle components that are damaged or no longer needed, as well as to eliminate harmful bacteria. NIDDK-supported research on this cellular degradation pathway has wide-reaching implications for understanding diseases within the Institute's mission. For example, the IBD Genetics Consortium identified mutations in an autophagy-related gene called *ATG16L1* that are associated with Crohn's disease. Further research showed that the protein encoded by this gene is important for intestinal cell secretion of granules containing antimicrobial agents, shedding light on how immune defenses are compromised in Crohn's disease. Studies of alpha-1 antitrypsin deficiency have shown that autophagy is important for degrading the mutant proteins that accumulate in the livers of individuals with this genetic disorder. Researchers have also found that red blood cell maturation relies on autophagy of mitochondria, and that disorders such as anemia can result when this process is compromised.

Gut Microbes in Health and Disease: The human digestive system is host to an enormous ecosystem of microorganisms, which is mostly beneficial but may occasionally be harmful. Bolstered by recent technological advances, NIDDK-supported researchers have been examining the composition of the microbial community in our intestines. By analyzing the bacterial genomes, collectively called the microbiome, scientists have uncovered a genomic view of the beneficial human-bacterial relationship that exists in the normal, healthy intestine. Scientists have also discovered that changes in the normal composition of the gut microbial community are associated with obesity, and that abnormal functioning of the human immune system in response to otherwise harmless gut microbes is

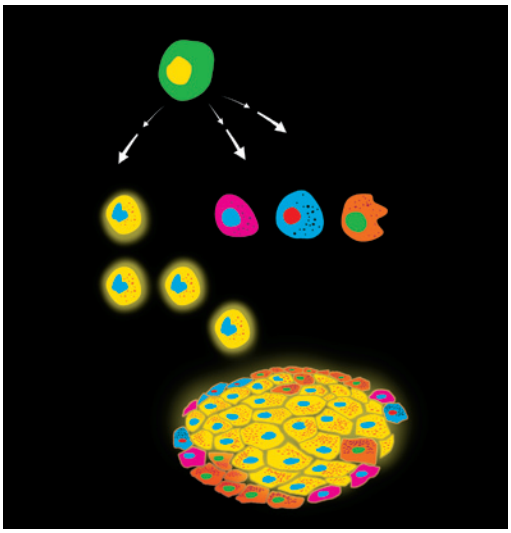


The human gut is home to a broad array of microscopic organisms that play an important role in human health and disease.
Image credit: Gross L. Human Gut Hosts a Dynamically Evolving Microbial Ecosystem. *PLoS Biology,* July 2007, vol. 5, issue 7, e199.

associated with inflammatory bowel diseases. NIDDK researchers have also discovered additional protective benefits of the normal gut microbial community in reducing infection by harmful bacteria and are investigating a possible role for gut microbes in reducing risk for type 1 diabetes. In addition to investigating bacteria in the intestines, NIDDK investigators have also studied *Helicobacter pylori* infection of the stomach. Recent advances have shown how the bacterium interacts with cells lining the stomach to alter their function, and how changes in the *H. pylori* genome are associated with progression from stomach inflammation to more serious inflammatory conditions and stomach cancer. Further NIDDK research efforts will continue to reveal new roles for gut microbial communities in normal health and disease.

RNAi-based Strategies for Metabolic and Inflammatory Diseases: Understanding the process by which the body can become resistant to the hormone insulin and the link between insulin resistance and the inflammatory response of the immune system is critical to developing effective therapeutics. NIDDK-supported scientists are utilizing a technique based on the phenomenon of ribonucleic acid interference (RNAi) both to identify factors involved in insulin resistance and the inflammatory response as well as for use as a potential therapy. In RNAi, molecules called "small interfering RNAs" reduce levels of specific proteins. Recently, investigators targeted a small interfering RNA to an inflammatory protein and administered this RNA to mice, using an innovative delivery vehicle. In doing so, they were able both to block the inflammatory response and alter the insulin resistance in obese mice. This research reveals the exciting potential for a new method of therapy for numerous diseases, including type 2 diabetes.

Stem Cells: Stem cells have the potential to develop into many different cell types in the body, and NIDDK-supported scientists continue to characterize their properties and seek potential new ways of using them to benefit patients. For example, researchers discovered a novel group of adult pancreatic progenitor cells that can generate insulin-producing beta cells, a finding with implications for future diabetes treatments. Scientists have also demonstrated that purified rat fetal stem cells transplanted into animals missing two-thirds of their livers are capable of fully repopulating this organ, lending support for the consideration of stem cell transplantation as an alternative to whole or partial liver



Stem cells can differentiate into a number of different cell types, a characteristic that may allow researchers to develop therapies for diseases in which tissues are damaged or malfunctioning.
Image credit: Donald Bliss, Medical Arts and Photography Branch, National Institutes of Health.

transplantation. Pursuing another avenue of research, and building on a landmark study on mouse cells by scientists in Japan, NIDDK-supported researchers showed that the insertion of just four defined genes into adult human skin cells could cause the cells to revert to a stem cell-like state, with characteristics closely resembling those of embryonic stem cells. Scientists have used this approach to generate stem cell lines from patients with different genetic diseases and disorders. These cells, known as induced pluripotent stem cells, or iPS cells, may provide insights into disease development, facilitate screening of candidate therapeutic agents, and, with further research progress, may one day yield cells for use in transplantation. These and other developments have the potential to lead to new cell-based therapies for a broad range of disorders.